Vena, D.
10/031092


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     (FILE 'REGISTRY' ENTERED AT 11:54:38 ON 26 MAY 2004)
                E PROTHROMBIN/CN
L1            6 S E3-E8
                E PROTHROMBINASE/CN 5
L2            7 S E3-E10
                E THROMBIN/CN
L3           32 S E3-E36

                E ACYL/CN 5
                E POLYETHYLENE GLYCOL/CN 5
L6            1 S E3
                E DICHLOROTRIAZINYLAMINOFLUORESCINYL/CN 5
L7            1 S E2
L8            2 S L6 OR L7

     FILE 'HCAPLUS' ENTERED AT 11:58:23 ON 26 MAY 2004
L1            6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (PROTHROMBIN/CN OR
                "PROTHROMBIN (CHICKEN CLONE PCII 203)"/CN OR "PROTHROMBIN
                 (HUMAN CLONE L(14,25,33,36,81) GENE F2)"/CN OR "PROTHROM
                BIN (OSTRICH)"/CN OR "PROTHROMBIN (RABBIT)"/CN OR
                "PROTHROMBIN (ZEBRAFISH)"/CN)
L2            7 SEA FILE=REGISTRY ABB=ON  PLU=ON  (PROTHROMBINASE/CN OR
                "PROTHROMBINASE (HUMAN CLONE HFGL2 GENE FGL2)"/CN OR
                "PROTHROMBINASE (HUMAN GENE FGL-2)"/CN OR "PROTHROMBINASE
                 (HUMAN GENE FGL2)"/CN OR "PROTHROMBINASE (MOUSE GENE
                FGL-2)"/CN OR "PROTHROMBINASE (MOUSE MACROPHAGE CLONE
                11-3-1 GENE MUSFIBLP)"/CN OR "PROTHROMBINASE (RATTUS
                NORVEGICUS STRAIN SPRAGUE-DAWLEY GENE FGL-2 SEQUENCE
                HOMOLOG)"/CN OR "PROTHROMBINASE (SWINE GENE FG12)"/CN)
L4        31184 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR PROTHROMBIN OR
                FACTOR(W)(2 OR II)
L5         1481 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND (L2 OR PROTHROMBI
                NASE)
L6            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "POLYETHYLENE GLYCOL"/C
                N
L7            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DICHLOROTRIAZINYLAMINOF
                LUORESCEIN/CN
L8            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 OR L7
L9           53 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L8 OR ACYL? OR
                ACETYL? OR SUCCINYL? OR MALEYL? OR (POLYETHYLENE OR POLY
                ETHYLENE)(W)GLYCOL OR PEG OR PYRIDOXAL(S)PHOSPHATE OR
                DICHLOROTRIAZIN? OR DI(W)(CHLOROTRIAZIN? OR CHLORO
                TRIAZIN?))
L10          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND (PLATELET OR
                PAS(S)PLATELET)

L10  ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2004 ACS on STN
ED   Entered STN:  23 Mar 2004
ACCESSION NUMBER:         2004:239275  HCAPLUS
DOCUMENT NUMBER:          140:268142
TITLE:                    Sphingolipids as Bioactive Regulators of
                          Thrombin Generation
AUTHOR(S):                Deguchi, Hiroshi; Yegneswaran, Subramanian;
                          Griffin, John H.
CORPORATE SOURCE:         Department of Molecular and Experimental
                          Medicine, The Scripps Research Institute, La
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Jolla, CA, 92037, USA
SOURCE: Journal of Biological Chemistry (2004), 279(13), 12036-12042
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sphingolipids contribute to modulation of two opposing cell processes, cell growth and apoptotic cell death; ceramide and sphingosine promote the latter and sphingosine-1-phosphate triggers the former. Thrombin, a pro-inflammatory protease that is regulated by the blood coagulation cascade, exerts similar effects depending on cell type. Here we report a new mechanism for cross-talk between sphingolipid metabolism and thrombin generation. Sphingosine and sphinganine, but not ceramide or sphingosine-1-phosphate, down-regulated thrombin generation on **platelet** surfaces (IC50 = 2.4 and 1.4 μM for sphingosine and sphinganine, resp.) as well as in whole plasma clotting assays. Thrombin generation was also inhibited by glucosylsphingosine, lysosphingomyelin, phytosphingosine, and primary alkylamines with >10 carbons. **Acylation** of the amino group ablated anticoagulant activities. Factor Va was required for the anticoagulant property of sphingosine because **prothrombin** activation was inhibited by sphingosine, sphinganine, and stearylamine in the presence but not in the absence of factor Va. Sphingosine did not inhibit thrombin generation when Gla-domainless factor Xa was used in **prothrombinase** assays, whereas sphingosine inhibited activation of Gla-domainless **prothrombin** by factor Xa/factor Va in the absence of phospholipids (IC50 = 0.49 μM). Fluorescence spectroscopy studies showed that sphingosine binds to fluorescein-labeled factor Xa and that this interaction required the Gla domain. These results imply that sphingosine disrupts interactions between factor Va and the Gla domain of factor Xa in the **prothrombinase** complex. Thus, certain sphingolipids may be bioactive lipid mediators of thrombin generation such that certain sphingolipid metabolites may modulate proteases that affect cell growth and death, blood coagulation, and inflammation.

IT **9002-05-5, Prothrombinase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(sphingosine disrupts interactions between factor Va and Gla domain of factor Xa in **prothrombinase** complex)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Nov 2002
ACCESSION NUMBER: 2002:907166 HCAPLUS
DOCUMENT NUMBER: 138:322
TITLE: Plasma glucosylceramide deficiency as risk factor for thrombosis and modulator of anticoagulant protein C
INVENTOR(S): Griffin, John H.; Deguchi, Hiroshi; Fernandez, Jose

PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002177563	A1	20021128	US 2002-86943	20020228
WO 2002102325	A2	20021227	WO 2002-US6340	20020228
WO 2002102325	A3	20030912		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1370570	A2	20031217	EP 2002-760992	20020228

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:
US 2001-272103P P 20010228
US 2001-278045P P 20010322
WO 2002-US6340 W 20020228

AB The present invention has determined that exogenously added glucosylceramide (GlcCer) and other neutral glycolipids such as the homologous Glc-containing globotriaosylceramide (Gb3Cer), dose-dependently prolonged clotting times of normal plasma in the presence but not absence of APC:protein S, indicating GlcCer or Gb3Cer can enhance protein C pathway anticoagulant activity. In studies using purified proteins, inactivation of factor Va by APC:protein S was enhanced by GlcCer alone and by GlcCer, globotriaosylceramide, lactosylceramide, and galactosylceramide in multicomponent vesicles containing phosphatidylserine and phosphatidylcholine. Thus, the present invention provides neutral glycolipids such as GlcCer and Gb3Cer, as anticoagulant cofactors that contribute to the antithrombotic activity of the protein C pathway. The present invention has also determined that a deficiency of plasma GlcCer is a risk factor for thrombosis. Methods are provided to determine individuals at risk for thrombosis, methods of treatment as well as methods of screening for antithrombotic factors from neutral glycolipids.

IT **72162-96-0, Prothrombinase**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(factor Va inactivation in antithrombotic neutral glycolipid screening; plasma glucosylceramide or other neutral glycolipid deficiency as risk factor for thrombosis and modulator of anticoagulant protein C)

IT **9001-26-7, Prothrombin 9002-05-5,** Blood

coagulation factor Xa
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(screening for antithrombotic neutral glycolipids in presence of; plasma glucosylceramide or other neutral glycolipid deficiency as risk factor for thrombosis and modulator of anticoagulant protein C)

L10 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 01 Feb 2002
ACCESSION NUMBER: 2002:85653 HCAPLUS
DOCUMENT NUMBER: 136:350356
TITLE: Anti-**platelet** and anti-thrombotic effects of triacetylshikimic acid in rats
AUTHOR(S): Huang, Fengyang; Xiu, Qiuping; Sun, Jianning; Hong, Enrique
CORPORATE SOURCE: Pharmacobiology Department, CINVESTAV-I.P.N., Mexico City, 14330, Mex.
SOURCE: Journal of Cardiovascular Pharmacology (2002), 39(2), 262-270
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because shikimic acid is the key intermediate in the shikimate pathway in plants and microorganisms, shikimic acid and its derivs. have been described as herbicides and anti-microbial agents. Triacetylshikimic acid (TSA) is an **acetylate** derivative of shikimic acid. The possible anti-**platelet** activity and anti-thrombotic efficacy of TSA were evaluated and its effect on arachidonic acid (AA) metabolism and second messengers including cAMP and cGMP was evaluated. After oral pretreatment with TSA, ADP-, collagen-, and AA-induced rat **platelet** aggregation was inhibited ex vivo in a dose-dependent manner. In an arteriovenous-shunt thrombosis model, oral administration of TSA resulted in a dose-dependent inhibition of thrombus growth. TSA markedly increased the cAMP level and showed no effect on the cGMP level in rat **platelets**. Also, no significant changes in ADP-induced thromboxane B2 formation in rat **platelets** or 6-ketoprostaglandin F1α production from the abdominal aorta were observed after oral administration of low and medium doses of TSA (12.5 and 50 mg/kg). Addnl., **prothrombin** time, activated partial thromboplastin time, and thrombin time were unchanged at effective anti-**platelet** doses of TSA. These results demonstrate that TSA exerts oral anti-**platelet** and anti-thrombotic efficacy without perturbation of systemic hemostasis in rats, which was partially concerned with the elevation of cAMP in **platelets**.

IT **9002-05-5**, Thromboplastin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activated partial; anti-**platelet** and anti-thrombotic effects of triacetylshikimic acid in rats)

IT **9001-26-7**, **Prothrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(time; anti-**platelet** and anti-thrombotic effects of triacetylshikimic acid in rats)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 21 Dec 2001
ACCESSION NUMBER: 2001:923801 HCAPLUS
DOCUMENT NUMBER: 136:42790
TITLE: Method for inactivation of microorganisms using photosensitizers
INVENTOR(S): Goodrich, Raymond Paul, Jr.; Hlavinka, Dennis
PATENT ASSIGNEE(S): Gambro, Inc., USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 19
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096340	A1	20011220	WO 2001-US18752	20010608
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1289991	A1	20030312	EP 2001-944414	20010608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-596429 A 20000615
WO 2001-US18752 W 20010608

AB Methods and apparatuses for treating fluids to inactivate microorganisms which may be present therein, said fluid containing one or more components selected from the group consisting of protein, blood and blood constituents are provided. The methods comprise adjusting the percentage of plasma in said fluid to a desired value; mixing an inactivation-effective, substantially non-toxic amount of an endogenous photosensitizer or endogenously-based derivative photosensitizer to said fluid; exposing said fluid to photoradiation of sufficient wavelength and energy to activate the photosensitizer, whereby said microorganisms are inactivated. Examples are provided dealing primarily with decontamination of blood supplies. Examples include a blood separation apparatus, a decontamination assembly, and methods for inactivation of bacteria, viruses, and bacteriophages in various blood prepns. using photosensitizers such as vitamin K5 and riboflavin. Effects of decontamination on **platelet** and red cell function were examined

IT **9001-26-7, Factor II 9002-05-5**

, Thromboplastin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inactivation of microorganisms in blood products using photosensitizers: effect on plasma proteins)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 26 Jan 2001
ACCESSION NUMBER: 2001:64135 HCAPLUS
DOCUMENT NUMBER: 134:112649
TITLE: Assay of the activation state of **platelets**
INVENTOR(S): Jesty, Jolyon; Bluestein, Danny
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005948	A1	20010125	WO 2000-US19239	20000714

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-143702P P 19990714
AB The invention provides for quant. measurement of an initial **platelet** activation state. In particular, the invention relates to a **platelet** activation assay that uses modified **prothrombin**, which is activated by **prothrombinase** and which generates thrombin that does not activate **platelets** but still retains proteolytic activity. In a specific example, **prothrombin acetylated** with sulfo-N-succinimidyl acetate generates thrombin in the presence of **prothrombinase**, in which the thrombin lacks **platelet** activating activity. Thrombin production is detected with a chromogenic peptide cleavage assay.
IT **9001-26-7DP, Prothrombin, acetylated**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(assay of the activation state of **platelets**)
IT **9001-26-7, Prothrombin 9002-05-5,** Blood coagulation factor Xa
RL: RCT (Reactant); RACT (Reactant or reagent)
(assay of the activation state of **platelets**)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 12 Oct 2000
ACCESSION NUMBER: 2000:720033 HCAPLUS
DOCUMENT NUMBER: 134:81238
TITLE: Prostaglandin E1 does not influence plasmatic coagulation, hepatic synthesis, or postoperative blood loss in patients after coronary-artery bypass grafting
AUTHOR(S): Locker, G. J.; Grimm, M.; Losert, H.; Stoiser, B.; Kofler, J.; Knapp, S.; Wilfing, A.; Knoebl, P.; Kapiotis, S.; Czerny, M.; Muhm, M.; Hiesmayr, M.; Frass, M.
CORPORATE SOURCE: Intensive Care Unit, Department of Internal Medicine I, University Hospital of Vienna, Vienna, Austria
SOURCE: Journal of Clinical Anesthesia (2000), 12(5), 363-370
CODEN: JCLBE7; ISSN: 0952-8180
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The study objective was to assess whether postoperatively administered prostaglandin E1 (PGE1) might prevent bleeding in patients after coronary artery bypass grafting (CABG). The design was a prospective, randomized, placebo-controlled trial in a university-affiliated hospital. Patients consisted of 49 patients scheduled for elective CABG surgery. The PGE1group received i.v. PGE1 up to 15 ng/kg/min for 72 h after surgery, whereas the placebo group received isotonic saline for the same time period. Nine patients (4 in the PGE1 group vs. 5 in the placebo group) had to be excluded because of hemodynamic instability, and 1 in the placebo group because of gastric bleeding. In the remaining 39 patients (20 vs. 19), no significant differences with regard to Hb levels or **platelet** count could be observed There was no significant difference between the groups concerning the amount of packed red blood cells, **platelet** concs., or fresh frozen plasma transfused. No significant differences could be observed regarding laboratory markers of coagulation activation or hepatic synthesis either. PGE1 did not prevent coagulation disturbances and blood loss when administered postoperatively in patients undergoing CABG. The absence of these expected effects might be explained by the concomitant administration of **acetylsalicylic** acid, whose antiaggregatory acivity seems to exceed the effects of PGE1.

IT **9001-26-7, Prothrombin 9002-05-5,** Thromboplastin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PGE1 effect on plasmatic coagulation, hepatic synthesis, and postoperative blood loss in humans after coronary-artery bypass grafting)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L10 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Aug 2000
ACCESSION NUMBER: 2000:533843 HCAPLUS
DOCUMENT NUMBER: 134:175168
TITLE: Effects of High-Molecular-Weight Cryoprotectants on **Platelets** and the Coagulation System
AUTHOR(S): Bakaltcheva, Irina; Ganong, Jason P.; Holtz, Bonnie L.; Peat, Raquel A.; Reid, Thomas
CORPORATE SOURCE: Transfusion and Homeostasis Medicine, Walter Reed Army Institute of Research, Silver Spring, MD, 20910, USA
SOURCE: Cryobiology (2000), 40(4), 283-293
CODEN: CRYBAS; ISSN: 0011-2240
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study is to examine the effects of the most widely used high-mol.-weight cryoprotectants on the coagulation system. Dextran, hydryoxyethyl starch (HES), polyvinyl pyrrolidone (PVP), **polyethylene glycol** (**PEG**), and albumin were added at different concns. in the range between 0.01-1% (w/v) to solvent/detergent-treated plasma. Using a STA/STA Compact coagulation analyzer the following clotting tests were performed: **prothrombin** time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), Factor V, and Factor VIII percentage of activity. PVP and **PEG** caused a significant increase in APTT, a decrease in Factor VIII percentage of activity, and a slight decrease in TT, while PT and Factor V percentage of activity remained unchanged. Dextran, HES, and albumin did not effect the clotting tests. The effect of high-mol.-weight cryoprotectants on **platelets** was assessed by **platelet**-induced clot retraction (PICR) and aggregation with thrombin and agglutination with ristocetin. **Platelet** aggregation and agglutination were unaffected by all cryoprotectants tested; however, PICR was significantly reduced in the presence of PVP or **PEG**. Possible mechanisms by which PVP and **PEG** interfere with the coagulation system are discussed. We also raise issues concerning the development of one-step blood cryopreservation techniques which do not require cryoprotectant removal prior to transfusion. (c) 2000 Academic Press.

IT **9002-05-5**, Thromboplastin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activated partial thromboplastin time; effects of high-mol.-weight cryoprotectants on **platelets** and coagulation system)

IT **25322-68-3, Polyethylene glycol**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(effects of high-mol.-weight cryoprotectants on **platelets** and coagulation system)

IT **9001-26-7, Prothrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(time; effects of high-mol.-weight cryoprotectants on **platelets** and coagulation system)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 Jul 1999
ACCESSION NUMBER: 1999:438363 HCAPLUS
DOCUMENT NUMBER: 131:269090
TITLE: **Acetylated Prothrombin** as a Substrate in the Measurement of the Procoagulant Activity of **Platelets**: Elimination of the Feedback Activation of **Platelets** by Thrombin
AUTHOR(S): Jesty, Jolyon; Bluestein, Danny
CORPORATE SOURCE: Program in Biomedical Engineering, State University of New York, Stony Brook, NY, 11794, USA
SOURCE: Analytical Biochemistry (1999), 272(1), 64-70
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human **prothrombin** was **acetylated** to produce a modified **prothrombin** that upon activation by **platelet**-bound **prothrombinase** generates a form of thrombin that does not activate **platelets** but retains its amidolytic activity on a chromogenic peptide substrate. If normal **prothrombin** is used in such an assay, the thrombin that is generated activates the **platelets** in a feedback manner, accelerating the rate of thrombin generation and thereby preventing accurate measurement of the initial **platelet** procoagulant activity. **Acetylation** of **prothrombin** was carried out over a range of concns. of sulfo-N-succinimidyl acetate (SNSA). **Acetylation** by 3 mM SNSA at room temperature for 30 min at pH 8.2 in the absence of metal ions produced a modified **prothrombin** that has <0.1% clotting activity (by specific **prothrombin** clotting assay), but it is activated by factor Xa (in the presence of either activated **platelets** or factor Va + anionic phospholipid) to produce thrombin activity that is measurable with a chromogenic substrate. Because the feedback action on the **platelets** is blocked, thrombin generation is linear, allowing quant. measurement of the initial **platelet** activation state. (c) 1999 Academic Press.
IT **9001-26-7D, Prothrombin, acetylated**
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**acetylated prothrombin** as a substrate in measurement of procoagulant activity of **platelets**)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Jan 1998

ACCESSION NUMBER: 1998:59 HCAPLUS
DOCUMENT NUMBER: 128:70385
TITLE: Rational Design and Synthesis of Novel, Potent Bis-phenylamidine Carboxylate Factor Xa Inhibitors
AUTHOR(S): Maduskuie, Thomas P., Jr.; McNamara, Kevin J.; Ru, Yu; Knabb, Robert M.; Stouten, Pieter F. W.
CORPORATE SOURCE: The DuPont Merck Pharmaceutical Company, DuPont Experimental Station E500/2401, Wilmington, DE, 19880-0500, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(1), 53-62
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mol. modeling studies, rational design, and synthesis of a novel series of bis-phenylamidine carboxylate compds. which are inhibitors of factor Xa in the blood coagulation cascade are described. Inhibition of blood coagulation has been proposed to have several potential therapeutic utilities (Kaiser and Hauptmann, Cardiovasc. Drug Rev. 1994, 12, 225-236). Factor Xa (fXa) holds a central position in the coagulation cascade (Coleman et al. in Hemostasis and Thrombosis: Basic Principles and Clin. Practice, 1994, pp 3-18). Its major role is the generation of thrombin by the proteolytic cleavage of **prothrombin**. Inhibition of fXa would serve to reduce the formation of **platelet** clots. The fXa dimer crystal structure (Tulinsky et al., J. Mol. Biol. 1993, 232, 947-966) was used in our mol. modeling studies to design a novel series of fXa inhibitors. We initially docked and minimized isolated small mol. fragments in the S1 and S4 aryl-binding subsites. Subsequently, these fragments were connected with a tether, so as not to disturb the orientation of the fragments in their resp. pockets. These modeling studies led to the initial compound which was found to have significant inhibitory potency for fXa (Ki = 34 nM). The synthesis of the core structure, structure-activity relationships (SAR), and proposed binding orientation based on mol. modeling for this novel bis-phenylamidine series of fXa inhibitors are described.

IT **9002-05-5**, Factor Xa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rational design and synthesis of novel potent bis-phenylamidine carboxylate factor Xa inhibitors)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 22 Oct 1997
ACCESSION NUMBER: 1997:667796 HCAPLUS
DOCUMENT NUMBER: 127:298722
TITLE: Pharmaceutical preparation for the treatment of blood coagulation disorders
INVENTOR(S): Turecek, Peter; Schwarz, Hans Peter; Eibl, Johann

PATENT ASSIGNEE(S): Immuno Aktiengesellschaft, Austria
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 796623	A2	19970924	EP 1997-890051	19970318
EP 796623	A3	20000517		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, IE, IT, LI, NL, SE				
AT 9600518	A	19980615	AT 1996-518	19960320
AT 404673	B	19990125		
AT 9601573	A	20000515	AT 1996-1573	19960904
AT 407116	B	20001227		
AT 408612	B	20020125	AT 1996-1673	19960920
AT 9700177	A	20010915	AT 1997-177	19970204
AT 408947	B	20020425		
CA 2200394	AA	19970920	CA 1997-2200394	19970319
AU 9716451	A1	19970925	AU 1997-16451	19970320
AU 725442	B2	20001012		
US 5866122	A	19990202	US 1997-821763	19970320
JP 10045620	A2	19980217	JP 1997-108013	19970321
US 6039945	A	20000321	US 1998-165745	19981006
US 6099837	A	20000808	US 1999-244762	19990205
US 6165974	A	20001226	US 1999-245339	19990205
US 6224862	B1	20010501	US 2000-521219	20000308
AU 763466	B2	20030724	AU 2000-71856	20001124

PRIORITY APPLN. INFO.:

AT 1996-518	A	19960320
AT 1996-1573	A	19960904
AT 1996-1673	A	19960920
AU 1997-16451	A3	19970320
US 1997-821763	A3	19970320
US 1998-165745	A3	19981006
US 1999-245339	A3	19990205

AB Patients with hemophilia A who develop inhibitory antibodies to coagulation factor VIII are effectively treated with a stable phospholipid-free composition containing a complex of ≥2 coagulation factors which are components of a **prothrombinase** or preprothrombinase; ≥1 of these factors must be activated. The factors may be selected from coagulation **factors II**, V, Va, X, and Xa, and are purified until free from endogenous phospholipids which might cause thromboembolic side effects. The composition is not subject to premature thrombin formation; thrombin is formed only at the site of bleeding as a result of contact with cellular phospholipids. Thus, a lyophilized fraction containing multiple coagulation factors was subjected to adsorption on Ca3(PO4)2, (NH4)2SO4 precipitation, and chromatog. on Sephadex G-25, and the coagulation factors were separated by ion-exchange chromatog. on DEAE-Sepharose FF; **factor II** was further purified by hydrophobic interaction chromatog. and ultrafiltration. A pharmaceutical formulation contained highly purified **factor II**, factor Xa, and antithrombin III in citrate buffer (pH 7.0) containing NaCl (8 g/L), and could be

lyophilized without significant loss of activity.

IT **9001-26-7P**, Blood-coagulation **factor II**
9002-05-5P, Blood-coagulation factor Xa **72162-96-0DP**
, **Prothrombinase**, precursors **72162-96-0P**,
Prothrombinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical preparation for treatment of blood coagulation disorders)

L10 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Jul 1995
ACCESSION NUMBER: 1995:696409 HCAPLUS
DOCUMENT NUMBER: 123:102787
TITLE: Calreticulin as antithrombotic agent
INVENTOR(S): Stern, David M.; Kuwabara, Keisuke; Benedict, Claude; Ryan, Jane
PATENT ASSIGNEE(S): Columbia University, USA; University of Texas System
SOURCE: U.S., 42 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5426097	A	19950620	US 1993-45261	19930406

PRIORITY APPLN. INFO.: US 1993-45261 19930406

AB A pharmaceutical composition is provided which comprises an amount of calreticulin effective for blocking or preventing thrombosis in a subject, causing substantially no defect or no defect in normal hemostasis, and a pharmaceutically effective carrier. The invention also provides a method for blocking or preventing thrombosis in a subject, causing substantially no defect or no defect in normal hemostasis; the method comprises administering calreticulin to the subject in an amount effective for blocking or preventing thrombosis. Also provided is a pharmaceutical composition comprising calreticulin in combination with an other antithrombotic agent, in an amount and proportion effective for enhancing the action of the other antithrombotic agent, to prevent clotting or dissolve clots which have already formed. The invention further provides a method for enhancing the action of another antithrombotic agent which prevents clotting or dissolve clots which have already formed; the method comprises administering to a subject calreticulin in combination with the other antithrombotic agent in an amount and proportion for enhancing the action of the other antithrombotic agent, to prevent clotting or dissolve clots which have already formed.

IT **9001-26-7**, **Prothrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calreticulin as antithrombotic agent, its isolation from bovine lung, and its characterization)

IT **9002-05-5,** Blood coagulation factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; calreticulin as antithrombotic agent, its isolation from bovine lung, its characterization, and its use with other agents)

L10 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 26 Nov 1994
ACCESSION NUMBER: 1994:650616 HCAPLUS
DOCUMENT NUMBER: 121:250616
TITLE: Dry chemistry cascade immunoassay and affinity assay
INVENTOR(S): Oberhardt, Bruce
PATENT ASSIGNEE(S): Cardiovascular Diagnostics, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9419690	A1	19940901	WO 1994-US1485	19940216
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2156174	AA	19940901	CA 1994-2156174	19940216
AU 9461734	A1	19940914	AU 1994-61734	19940216
AU 689768	B2	19980409		
EP 685069	A1	19951206	EP 1994-908755	19940216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08507148	T2	19960730	JP 1994-519035	19940216
IL 108699	A1	19970610	IL 1994-108699	19940217
US 5601991	A	19970211	US 1995-387373	19950213
US 5677133	A	19971014	US 1996-712370	19960911
PRIORITY APPLN. INFO.:			US 1993-18415	19930217
			WO 1994-US1485	19940216
			US 1995-387373	19950213

AB A method is described for performing an affinity assay comprising contacting a sample to be assayed for the presence of an analyte with a dry reagent containing the analyte (hapten, antigen, antibody, receptor, or complementary polynucleotide) bound to a reaction cascade initiator, an antibody or other binding pair partner reactive with the analyte, and magnetic particles, to form an assay mixture in a reaction chamber; incubating the assay mixture; applying an oscillating or moving static magnetic field to the assay mixture; activating the reaction cascade initiator to initiate a reaction cascade; monitoring the response of the magnetic particles to the oscillating or moving static magnetic field to provide a time varying signal; and determining the analyte concentration of the sample by anal.
of the time varying signal. Also described are a kit for performing the assay and a diagnostic system for performing the assay. A dry chemical reaction slide was prepared and tested using a blood coagulation

cascade system in a magnetic particle interrogation system. As little as 1 nM thrombin could be detected. Views of the apparatus are shown.

IT **9002-05-5D**, Factor Xa, analyte conjugates
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(as reaction cascade initiator; in dry chemical cascade immunoassay and affinity assay)

IT **9002-05-5D**, Factor Xa, conjugates
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(in dry chemical cascade immunoassay and affinity assay)

IT **25322-68-3, Polyethylene glycol**
RL: ARU (Analytical role, unclassified); DEV (Device component use); ANST (Analytical study); USES (Uses)
(in dry chemical cascade immunoassay and affinity assay)

IT **9001-26-7, Prothrombin**
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(reaction cascade component; in dry chemical cascade immunoassay and affinity assay)

L10 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 13 Dec 1992
ACCESSION NUMBER: 1992:626046 HCAPLUS
DOCUMENT NUMBER: 117:226046
TITLE: Antiplatelet drugs and generation of thrombin in clotting blood
AUTHOR(S): Szczeklik, A.; Krzanowski, M.; Gora, P.; Radwan, J.
CORPORATE SOURCE: Dep. Med., Copernicus Acad. Med., Krakow, 31-066, Pol.
SOURCE: Blood (1992), 80(8), 2006-11
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Platelets** participate in formation of thrombin through secretion of coagulation factors and by providing a catalytic surface on which **prothrombinase** complex is assembled. The authors studied the effects of four antiplatelet drugs on thrombin formation in healthy volunteers. Thrombin generation was monitored both in vitro-in recalcified plasma-and ex vivo-in blood emerging from a standardized skin microvasculature injury, which also served to determine bleeding time. A math. model has been developed to describe the latter reaction. It is based on estimation of the rate of increase of fibrinopeptide A (FPA), a specific marker of thrombin activity, in blood emerging from skin incisions. Two hours after the ingestion of 500 mg of aspirin, thrombin formation became significantly impaired both in vitro and ex vivo. In contrast, 2 h after the oral administration of placebo, indomethacin 50 mg, or OKY-046 (a thromboxane synthase inhibitor) 400 mg, thrombinogenesis remained unaltered. Ticlopidine, studied either 3 h after 500 mg oral administration, or after 5 days of intake at a daily dose of 500 mg, had no effect on thrombin generation. Thus, aspirin, contrary to other antiplatelet drugs, depresses thrombin formation in clotting blood, a phenomenon that might be of clin. relevance.

It is suggested that aspirin exerts this effect by **acetylating prothrombin** and/or macromols. of **platelet** membrane.

L10 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Nov 1990
ACCESSION NUMBER: 1990:565420 HCAPLUS
DOCUMENT NUMBER: 113:165420
TITLE: Anticoagulant activity of hirudin peptides, and their therapeutic use and preparation
INVENTOR(S): Maraganore, John M.
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: Eur. Pat. Appl., 41 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 333356	A2	19890920	EP 1989-302160	19890303
EP 333356	A3	19901219		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 8930982	A1	19890907	AU 1989-30982	19890303
WO 9003391	A1	19900405	WO 1989-US848	19890424
W: DK, FI, HU, JP, KR, NO				
HU 55799	A2	19910628	HU 1989-4117	19890424
JP 04500802	T2	19920213	JP 1989-507630	19890424
NO 9003833	A	19901102	NO 1990-3833	19900903
DK 9002105	A	19910327	DK 1990-2105	19900903
US 5256559	A	19931026	US 1991-677609	19910327

PRIORITY APPLN. INFO.:
US 1988-164178 19880304
US 1988-251150 19880929
US 1988-280618 19881205
US 1989-314755 19890228
WO 1989-US848 19890424

OTHER SOURCE(S): MARPAT 113:165420

AB Hirudin-related peptides, e.g. Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-X (X = CO2H, Leu, or Leu-Gln), show anticoagulant activity. The peptides are homologous to at least a portion of the C-terminal 26 amino acids of hirudin, may be characterized by having a modified tyrosine residue, and are used for therapy, prophylaxis and diagnosis. Covalent and peptidomimetic analogs of the peptide also display anticoagulant activity. Novel methods for sulfating a tyrosine residue of a peptide or polypeptide also are claimed. Thus, the anticoagulant activity of sulfo-Tyr63hirudin53-64 was demonstrated in an in vitro assay in which the peptide inhibited thrombin activity as measured by the inhibition of activated partial thromboplastin time. Hirudin53-64 was used as control test substance.

IT **9001-26-7, Prothrombin**
RL: BIOL (Biological study)
(activation of, by factor Xa, sulfo-Tyr63 hirudin53-64 inhibition of)

IT **9002-05-5**, Blood-coagulation factor Xa

RL: PROC (Process)
(inhibition of, by hirudin peptides)
IT **25322-68-3DP**, conjugates with sulfo-Tyr63hirudin53-64
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, anticoagulant activity in relation to)

L10 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 22 Mar 1986
ACCESSION NUMBER: 1986:84047 HCAPLUS
DOCUMENT NUMBER: 104:84047
TITLE: Comparison of the abilities of synthetic and **platelet**-derived membranes to enhance thrombin formation
AUTHOR(S): Jones, Marcie E.; Lentz, Barry R.; Dombrose, Frederick A.; Sandberg, Helena
CORPORATE SOURCE: Cent. Throm. Hemostasis, Univ. North Carolina, Chapel Hill, NC, 27514, USA
SOURCE: Thrombosis Research (1985), 39(6), 711-24
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relative abilities of blood **platelet**-derived membranes and synthetic phospholipid vesicles to enhance the **prothrombinase**-catalyzed conversion of **prothrombin** to thrombin were determined For each type of membrane, the maximum amount of thrombin formed as a function of amount of available lipid was measured by using a chromogenic substrate assay. The lipid concentration at which the amount of thrombin formed began to exceed that formed in the absence of lipid (critical phospholipid concentration) was used to compare the surfaces' abilities to support thrombin formation. For **platelet**-derived membranes and for equimolar, charged-lipid/phosphatidylcholine (PC) vesicles, the critical concns. increased in the following order: **platelet**-derived membranes .simeq. phosphatidylserine (PS) .simeq. phosphatidic acid (PA) << monomethyl PA and monoethyl PA << phosphatidylinositol and phosphatidylglycerol. For mixed anionic/neutral lipid vesicles above their phase transitions, measured critical concns. were relatively insensitive to changes in lipid **acyl** chains, the neutral lipid component, and membrane curvature, but were sensitive to changes in the anionic lipid content of the mixts. Comparison of these data suggested that equimolar PS/PC and PA/PC vesicles can emulate reasonably well the thrombin-generating ability of **platelet**-derived membranes.
IT **72162-96-0**
RL: BIOL (Biological study)
(thrombin formation by, in membrane presence, membrane composition effect on)

L10 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1984:20959 HCAPLUS
DOCUMENT NUMBER: 100:20959
TITLE: Fibrinogen interaction with human **platelets**: effect of other coagulation

factors, prostaglandins and **platelet** inhibitors
AUTHOR(S): Al-Mondhiry, Hamid; Ballard, James O.; McGarvey, Virginia
CORPORATE SOURCE: Coll. Medic., Pennsylvania State Univ., Hershey, PA, 17033, USA
SOURCE: Thrombosis Research (1983), 31(3), 415-26
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of clotting factors on 125I-labeled fibrinogen (fg) binding to gel filtered human **platelets** was investigated. The action of exogenously added or endogenously synthesized prostaglandins and the effect of antiplatelet drugs were also investigated. **Prothrombin** and active factor X enhance ADP-induced **platelet**-fg binding, whereas active factor VIII and active factor IX, sep. or combined, are without effect. Human **prothrombin** complex (PC) factor concs. (II-VII-IX-X) cause significant enhancement of **platelet**-fg binding; this effect is most likely due to activated factors and (or) traces of thrombin present in the preparation In the concentration used, these clotting factors and the PC factor concs. failed to aggregate **platelets** in **platelet**-rich plasma. **Acetylsalicylic** acid, carbenicillin, and the Ca2+ channel-blocking agents verapamil and nifedipine showed variable degrees of inhibition of ADP-induced **platelet**-fg binding. Chlorpromazine and propranolol were without effect. Estrogen and progesterone had some enhancing effect on binding. Evidently, when the hemostatic mechanism is initiated, TXA2 synthesis and activated **prothrombin** complex factors significantly enhance fg binding to **platelets**, a key step in hemostasis. Inhibitors of aggregation do not necessarily impede **platelet**-fibrinogen interaction.

IT **9001-26-7 9002-05-5**
RL: BIOL (Biological study)
(fibrinogen interaction with human blood **platelet** in relation to)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:01:21 ON 26 MAY 2004)
L11 28 S L10
L12 19 DUP REM L11 (9 DUPLICATES REMOVED)

L12 ANSWER 1 OF 19 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004141156 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14722105
TITLE: Sphingolipids as bioactive regulators of thrombin generation.
AUTHOR: Deguchi Hiroshi; Yegneswaran Subramanian; Griffin John H
CORPORATE SOURCE: Department of Molecular and Experimental Medicine, The Scripps Research Institute, MEM 180, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.
CONTRACT NUMBER: R01 HL 21544 (NHLBI)
SOURCE: Journal of biological chemistry, (2004 Mar 26) 279

(13) 12036-42.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040323
Last Updated on STN: 20040510
Entered Medline: 20040507

AB Sphingolipids contribute to modulation of two opposing cell processes, cell growth and apoptotic cell death; ceramide and sphingosine promote the latter and sphingosine-1-phosphate triggers the former. Thrombin, a pro-inflammatory protease that is regulated by the blood coagulation cascade, exerts similar effects depending on cell type. Here we report a new mechanism for cross-talk between sphingolipid metabolism and thrombin generation. Sphingosine and sphinganine, but not ceramide or sphingosine-1-phosphate, down-regulated thrombin generation on **platelet** surfaces (IC(50) = 2.4 and 1.4 microm for sphingosine and sphinganine, respectively) as well as in whole plasma clotting assays. Thrombin generation was also inhibited by glucosylsphingosine, lysosphingomyelin, phytosphingosine, and primary alkylamines with >10 carbons. **Acylation** of the amino group ablated anticoagulant activities. Factor Va was required for the anticoagulant property of sphingosine because **prothrombin** activation was inhibited by sphingosine, sphinganine, and stearylamine in the presence but not in the absence of factor Va. Sphingosine did not inhibit thrombin generation when Gla-domainless factor Xa was used in **prothrombinase** assays, whereas sphingosine inhibited activation of Gla-domainless **prothrombin** by factor Xa/factor Va in the absence of phospholipids (IC(50) = 0.49 microm). Fluorescence spectroscopy studies showed that sphingosine binds to fluorescein-labeled factor Xa and that this interaction required the Gla domain. These results imply that sphingosine disrupts interactions between factor Va and the Gla domain of factor Xa in the **prothrombinase** complex. Thus, certain sphingolipids may be bioactive lipid mediators of thrombin generation such that certain sphingolipid metabolites may modulate proteases that affect cell growth and death, blood coagulation, and inflammation.

L12 ANSWER 2 OF 19 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2004:103294 SCISEARCH
THE GENUINE ARTICLE: 764MU
TITLE: Unique in vivo modifications of coagulation factor V produce a physically and functionally distinct **platelet**-derived cofactor - Characterization of purified **platelet**-derived factor V/Va
AUTHOR: Gould W R; Silveira J R; Tracy P B (Reprint)
CORPORATE SOURCE: Univ Vermont, Coll Med, Dept Biochem, Given Bldg, Rm C409, 89 Beaumont Ave, Burlington, VT 05405 USA (Reprint); Univ Vermont, Coll Med, Dept Biochem, Burlington, VT 05405 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (23 JAN 2004) Vol.

279, No. 4, pp. 2383-2393.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 72

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Platelet**- and plasma-derived factor Va (FVa) serve essential cofactor roles in **prothrombinase**-catalyzed thrombin generation. **Platelet**- derived FV/Va, purified from Triton X-100 **platelet** lysates was composed of a mixture of polypeptides ranging from similar to 40 to 330 kDa, mimicking those visualized by Western blotting of **platelet** lysates and releasates with anti-FV antibodies. The purified, **platelet**-derived protein expressed significant cofactor activity such that thrombin activation led to only a 2-3-fold increase in cofactor activity yet expression of a specific activity identical to that of purified, plasma-derived FVa. Physical and functional differences between the two cofactors were identified. Purified, **platelet**-derived FVa was 2-3-fold more resistant to activated protein C-catalyzed inactivation than purified plasma-derived FVa on the thrombin-activated **platelet** surface. The heavy chain subunit of purified, **platelet** -derived FVa contained only a fraction (similar to 10 - 15%) of the intrinsic phosphoserine present in the plasma-derived FVa heavy chain and was resistant to phosphorylation at Ser(692) catalyzed by either casein kinase II or thrombin-activated **platelets.** MALDI-TOF mass spectrometric analyses of tryptic digests of **platelet**-derived FV peptides detected an intact heavy chain uniquely modified on Thr(402) with an N-**acetylglucosamine** or N-**acetylgalactosamine,** whereas Ser(692) remained unmodified. N-terminal sequencing and MALDI-TOF analyses of **platelet**-derived FV/Va peptides identified the presence of a full-length heavy chain subunit, as well as a light chain subunit formed by cleavage at Tyr(1543) rather than Arg(1545) accounting for the intrinsic levels of cofactor activity exhibited by native **platelet**-derived FVa. These collective data are the first to demonstrate physical differences between the two FV cofactor pools and support the hypothesis that, subsequent to its endocytosis by megakaryocytes, FV is modified to yield a **platelet**-derived cofactor distinct from its plasma counterpart.

L12 ANSWER 3 OF 19 EMBASE on STN

ACCESSION NUMBER: 2004099805 EMBASE
TITLE: Current Concepts of Hemostasis: Implications for Therapy.
AUTHOR: Roberts H.R.; Monroe D.M.; Escobar M.A.
CORPORATE SOURCE: Dr. H.R. Roberts, Hematology/Oncology Division, Univ. of N. Carolina Sch. of Med., 932 Mary Ellen Jones Bldg./CB #7035, Chapel Hill, NC 27599-7035, United States. hrr@med.unc.edu
SOURCE: Anesthesiology, (2004) 100/3 (722-730).
Refs: 30

ISSN: 0003-3022 CODEN: ANESAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The revised model of coagulation has implications for therapy of both hemorrhagic and thrombotic disorders. Of particular interest to anesthesiologists is the management of clotting abnormalities before, during, and after surgery. Most hereditary and acquired coagulation factor deficiencies can be managed by specific replacement therapy using clotting factor concentrates. Specific guidelines have also been developed for perioperative management of patients using anticoagulant agents that inhibit **platelet** or coagulation factor functions. Finally, recombinant factor VIIa has been used off-label as a hemostatic agent in some surgical situations associated with excessive bleeding that is not responsive to conventional therapy.

L12 ANSWER 4 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004089387 EMBASE
TITLE: Sustained elevated amounts of circulating procoagulant membrane microparticles and soluble GPV after acute myocardial infarction in diabetes mellitus.
AUTHOR: Morel O.; Hugel B.; Jesel L.; Lanza F.; Douchet M.-P.; Zupan M.; Chauvin M.; Cazenave J.-P.; Freyssinet J.-M.; Tori F.
CORPORATE SOURCE: F. Toti, Inst. d'Hematologie et d'Immunologie, Faculte de Medecine, 4 rue Kirschleger, 67085 Strasbourg Cedex, France. Florence.Toti@hemato-ulp.u-strasbg.fr
SOURCE: Thrombosis and Haemostasis, (2004) 91/2 (345-353). Refs: 45
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB During myocardial infarction (MI), **platelet** activation and endothelial apoptosis are responsible for the release of procoagulant membrane-derived microparticles (MP) in the blood flow. MP prothrombotic and proinflammatory properties may be crucial for coronary prognosis. Elevated amounts of circulating procoagulant MP were described in diabetes mellitus (DM), and could be of particular significance in a MI context. We evaluated the prothrombotic status of DM and non-DM (NDM) patients at days 1 and 6 after MI, by

measurement of circulating procoagulant MP and soluble GPV (sGPV), the **platelet** glycoprotein V major fragment released upon thrombin cleavage. Variations were compared to values measured in healthy volunteers (HV). Procoagulant MP were captured onto insolubilized annexin V and quantified by **prothrombinase** assay. Their cellular origin was assessed.With respect to HV,the levels of procoagulant MP detected at D1 and D6 were elevated in DM and NDM, MP being significantly higher in DM vs. NDM. The high amounts of **platelet**-derived MP and the correlation between procoagulant MP and sGPV, testify to the central role of thrombin-activated **platelets** during MI in both DM and NDM subsets. The release of **platelet** and endothelial cell-derived MP persisted at D6 and was more important in DM, the associated prothrombotic risk being also reflected by higher levels of sGPV. The endothelial damage revealed by endothelial-derived MP was twice that observed in NDM patients. In DM patients presenting cardiovascular events at 6 month follow-up, MP levels were significantly higher at D1 after MI than in those without complication (24.9 ± 4.8 vs. 12.3 ± 2.7 nM PhtdSer, p = 0.02), suggesting a prognostic potential for MP.

L12 ANSWER 5 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004146569 EMBASE

TITLE: [**Platelet** aggregation and antiplatelet agents in acute coronary syndromes]. L'AGREGATION PLAQUETTAIRE ET SES INHIBITEURS DANS LES SYNDROMES CORONARIENS AIGUS.

AUTHOR: Collet J.-P.; Choussat R.; Montalescot G.

CORPORATE SOURCE: J.-P. Collet, Institut de Cardiologie, Hopital de la Pitie-Solpetriere, 47, boulevard de l'Hopital, 75013 Paris, France. jean-philippe.collet@psl.ap-hop-paris.fr

SOURCE: Medecine/Sciences, (2004) 20/3 (291-297).
Refs: 28
ISSN: 0767-0974 CODEN: MSMSE4

COUNTRY: France

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT:
006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: French

SUMMARY LANGUAGE: English; French

AB Antiplatelet agents are the cornerstone therapy of acute coronary syndromes. In the setting of ST elevation myocardial infarction, antiplatelet therapy prevent the prothrombotic effect of reperfusion therapy including thrombolysis and primary percutaneous coronary intervention. In non ST-elevation acute coronary syndromes, antiplatelet therapy prevent s complete coronary thrombotic occlusion and therefore the occurrence of ST elevation myocardial infarction. Antiplatelet agent benefit is related to the patient's risk profile. It is well established that combined antiplatelet therapy is the most effective in high risk patients. Several

important issues have to be faced including the identification of non responders, dose adjustment and the management of temporary interruption of antiplatelet agents in stable coronary artery disease patients.

L12 ANSWER 6 OF 19 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-147335 [15] WPIDS
DOC. NO. NON-CPI: N2001-107848
DOC. NO. CPI: C2001-043641
TITLE: Determining activation state of **platelets**, useful for assessing risk of thrombotic disease, comprises measuring conversion of modified **prothrombin** to a thrombin that can not activate **platelets**.
DERWENT CLASS: A96 B04 D16 S03
INVENTOR(S): BLUESTEIN, D; JESTY, J
PATENT ASSIGNEE(S): (UYNY) UNIV NEW YORK STATE RES FOUND
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001005948	A1	20010125	(200115)*	EN	34
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000062142	A	20010205	(200128)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001005948	A1	WO 2000-US19239	20000714
AU 2000062142	A	AU 2000-62142	20000714

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000062142	A	Based on	WO 2001005948

PRIORITY APPLN. INFO: US 1999-143702P 19990714
AN 2001-147335 [15] WPIDS
AB WO 200105948 A UPAB: 20010317
NOVELTY - The activation state of **platelets** is assayed by detecting conversion of a modified **prothrombin** substrate (I) to a modified product (II), catalyzed by a **platelet**-associated **prothrombinase** (pT).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit for this assay, comprising (I) and a system for detecting (II).

USE - The method is useful for detecting or quantifying **platelet** activation, for evaluating the thrombotic potential

of a subject, particularly where biomedical devices that recirculate blood are being used, but also for direct measurements on **platelets**. The measured level of activation can be used to select appropriate management or therapeutic regimes for thrombotic diseases, or to confirm that thrombotic potential is adequate for therapeutic clotting, e.g. in patients about to undergo surgery.

ADVANTAGE - (I) generates a modified thrombin that retains proteolytic activity (for detection) but does not cause feedback activation of **platelets**. Therefore, a more accurate assay is provided, since the rate of thrombin generation will be linear. The method is fast and simple, and less expensive than fluorescence-activated cell sorting, which is the current standard for measuring **platelet** activation.

Dwg.0/4

L12 ANSWER 7 OF 19 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:822277 SCISEARCH
THE GENUINE ARTICLE: 482PG
TITLE: Blood coagulation at the site of microvascular injury: effects of low-dose aspirin
AUTHOR: Undas A; Brummel K; Musial J; Mann K G (Reprint); Szczeklik A
CORPORATE SOURCE: Univ Vermont, Dept Biochem, Given Bldg, Rm E407, Burlington, VT 05405 USA (Reprint); Univ Vermont, Dept Biochem, Burlington, VT 05405 USA; Jagiellonian Univ, Sch Med, Dept Med, Krakow, Poland
COUNTRY OF AUTHOR: USA; Poland
SOURCE: BLOOD, (15 OCT 2001) Vol. 98, No. 8, pp. 2423-2431. Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA. ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 56

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The sequence of coagulant reactions in vivo following vascular injury is poorly characterized. Using quantitative immunoassays, the time courses were evaluated for activation of **prothrombin**, factor (F)V, FXIII, fibrinogen (Fbg) cleavage, and FVa inactivation in bleeding-time blood collected at 30-second intervals from 12 healthy subjects both before and after aspirin ingestion. **Prothrombin** decreased at a maximum rate of 14.2 +/- 0.6 nM per second to 10% of initial values at the end of bleeding. Significant amounts of a-thrombin B chain appeared rapidly at 90 seconds of bleeding and increased at a maximum rate of 0.224 +/- 0.03 nM per second to a peak value of 38 nM. Kinetics of prethrombin 2 generation was almost identical. **Prothrombinase** concentration reached a peak value of 22 pM at 150 seconds and then decreased to 9 pM at the end of bleeding. **Prothrombin** fragment 1.2 (F1.2) was produced explosively (0.673 +/- 0.05 nM per second), whereas thrombin-antithrombin III (TAT) complexes were generated at a much slower rate (0.11 +/- 0.008 nM per second; P =.002). FVa light chain was detectable 30 seconds later than the heavy chain (150 seconds) and was produced at a slightly slower rate (0.027 +/- 0.001 nM per second) when compared with the heavy chain (0.032 +/- 0.002 nM per second; P =.041). The 30 000 fragment

(residues 307-506) of FVa heavy chain produced by activated protein C appeared as early as at 90 seconds and increased with time. Fbg was removed from the blood shed with a high rate of 0.047 +/- 0.02 muM/s and became undetectable at approximately 180 seconds of bleeding. The velocity of FXIII activation correlated with thrombin B-chain formation. A 7-day aspirin administration (75 mg/d) resulted in significant reductions in maximum rates of (1) **prothrombin** removal (by 29%; P =.008); generation of alpha -thrombin B-chain (by 27.2%; P =.022), and prethrombin 2 (by 26%; P=.014); formation of F1.2 (by 31.4%; P =.009) and TAT (by 30.3%; P = 0.013); (2) release of FVa heavy chain (by 25%; P =.003) and FVa light chain (by 29.6%; P =.007); (3) Fbg depletion from solution (by 30.5%; P =.002); and (4) FXIII activation (by 28.6%; P =.003). Total amounts of the proteins studied, collected at every interval, also significantly decreased following aspirin ingestion. These results indicate that low-dose aspirin impairs thrombin generation and reactions catalyzed by this enzyme at the site of the injury. (C) 2001 by The American Society of Hematology.

L12 ANSWER 8 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1999:365715 BIOSIS
DOCUMENT NUMBER: PREV199900365715
TITLE: Intravenous paraoxon (POX) exposure: Coagulation studies in mini pigs.
AUTHOR(S): Petroianu, Georg [Reprint author]; Toomes, Mia; Maleck, Wolfgang; Bergler, Wolfgang; Ruefer, Roderich
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Heidelberg at Mannheim, Maybach Street 14-16, 68169, Mannheim, Germany
SOURCE: Chemico-Biological Interactions, (May 14, 1999) Vol. 119-120, No. 0, pp. 489-495. print.
CODEN: CBINA8. ISSN: 0009-2797.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Sep 1999
Last Updated on STN: 2 Sep 1999

AB The in vivo effects of the organophosphorus compound (OPC) paraoxon (POX) on blood coagulation of mini pigs were assessed by measuring the partial thromboplastin time (PTT), **prothrombin** time (PT), fibrinogen, factor V, factor VII, factor VIII, antithrombin III, protein C, and **platelet** count. The mini pigs were randomly assigned to a POX-treatment group (n = 9) receiving 54 mg POX kg-1 BW-1 or the control group (n = 9). Measurements were carried out over a period of 150 min after poisoning. The exposure to POX did not have any influence on measurements of PT, factor VIII, factor VII, factor V, antithrombin III, protein C, or fibrinogen compared to the control group evaluated by rank order test (ROT) during the time of observation (150 min). Changes seen in the intrinsic coagulation followed a biphasic pattern corresponding to an early sympathomimetic phase with PTT-shortening and a decrease of the **platelet** count, and a late vagal phase, with PTT-prolongation. The hypercoagulability seen in the sympathomimetic phase is probably due to a massive release of catecholamines from the adrenals. Previous studies showed in vitro no coagulation activating effect of POX. The hypocoagulability in

the vagal phase shown by the PTT-prolongation is probably due to POX influencing **platelet** function or its inhibition of clotting factors, which are serine proteases, or a combination of the two.

L12 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:595133 SCISEARCH
THE GENUINE ARTICLE: 219QP
TITLE: Complement-induced procoagulant alteration of red blood cell membranes with microvesicle formation in paroxysmal nocturnal haemoglobinuria (PNH): implication for thrombogenesis in PNH
AUTHOR: Ninomiya H (Reprint); Kawashima Y; Hasegawa Y; Nagasawa T
CORPORATE SOURCE: UNIV TSUKUBA, DIV HAEMATOL, INST CLIN MED, TENNODAI 1-1-1, TSUKUBA, IBARAKI 3058575, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, (JUL 1999) Vol. 106, No. 1, pp. 224-231.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0007-1048.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Complement-induced procoagulant alteration of red blood cell (RBC) membranes in paroxysmal nocturnal haemoglobinuria (PNH) was examined, Microvesicles, deficient in **acetylcholinesterase**, were generated and released from PNH RBC upon complement activation. The microvesicles generated from complement-activated PNH RBC accelerated factor Xa-dependent plasma coagulation more than those generated from RBC by the treatment with ionophore A23187. When assessed by factor Xa-catalysed **prothrombin** activation, complement activation enhanced procoagulant properties of both normal and PNH RBC similarly, although PNH RBC were lysed but normal RBC were not. This enhancement of factor Xa-dependent **prothrombinase** activity of complement-activated RBC was inhibited by the treatment of the RBC with annexin V, a protein with binding affinity for anionic phospholipids especially for phosphatidylserine (PS). Neither the enhanced procoagulant properties of RBC nor apparent RBC population with annexin V-binding affinity were demonstrated before complement activation in any of the four PNH patients studied. PS-externalized PNH RBC and microvesicles may contribute to the removal of PNH RCC from the circulation, We conclude that although PNH RBC do not constantly exhibit enhanced procoagulant properties in vivo, complement activation induces a procoagulant alteration of RBC membranes with microvesicle formation, potentially contributing to the thrombogenesis in PNH.

L12 ANSWER 10 OF 19 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1999335340 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10405294
TITLE: **Acetylated prothrombin** as a

substrate in the measurement of the procoagulant activity of **platelets**: elimination of the feedback activation of **platelets** by thrombin.

AUTHOR: Jesty J; Bluestein D

CORPORATE SOURCE: Schools of Engineering and Medicine, State University of New York, Stony Brook, New York 11794, USA.

SOURCE: Analytical biochemistry, (1999 Jul 15) 272 (1) 64-70. Journal code: 0370535. ISSN: 0003-2697.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199909

ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990910

AB Human **prothrombin** was **acetylated** to produce a modified **prothrombin** that upon activation by **platelet**-bound **prothrombinase** generates a form of thrombin that does not activate **platelets** but retains its amidolytic activity on a chromogenic peptide substrate. If normal **prothrombin** is used in such an assay, the thrombin that is generated activates the **platelets** in a feedback manner, accelerating the rate of thrombin generation and thereby preventing accurate measurement of the initial **platelet** procoagulant activity. **Acetylation** of **prothrombin** was carried out over a range of concentrations of sulfo-N-succinimidyl acetate (SNSA). **Acetylation** by 3 mM SNSA at room temperature for 30 min at pH 8.2 in the absence of metal ions produced a modified **prothrombin** that has <0.1% clotting activity (by specific **prothrombin** clotting assay), but it is activated by factor Xa (in the presence of either activated **platelets** or factor Va + anionic phospholipid) to produce thrombin activity that is measurable with a chromogenic substrate. Because the feedback action on the **platelets** is blocked, thrombin generation is linear, allowing quantitative measurement of the initial **platelet** activation state.

L12 ANSWER 11 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998201471 EMBASE

TITLE: Prolonged activation of **prothrombin** on the vascular wall after arterial injury.

AUTHOR: Ghigliotti G.; Waissbluth A.R.; Speidel C.; Abendschein D.R.; Eisenberg P.R.

CORPORATE SOURCE: Dr. P.R. Eisenberg, Cardiovascular Division, Campus Box 80156, Washington Univ. School of Med., 660 S Euclid, St Louis, MO 63110, United States. eisenber@im.wusti.edu

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology, (1998) 18/2 (250-257).
Refs: 48
ISSN: 1079-5642 CODEN: ATVBFA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This study was designed to characterize the relative roles of bound Xa/Va and thrombin activity in vascular wall procoagulant activity after balloon-induced injury and the extent to which intravenous aspirin and heparin attenuate procoagulant activity associated with the vascular wall. Abdominal aortic injury was induced in rabbits by overinflation and multiple passages of a 4F embolectomy catheter. Rabbits were killed 15 minutes or 4, 8, 24, 48, 72, 96, or 120 hours after injury. Aortic segments were incubated ex vivo to define bound procoagulant activity. Thrombin activity bound to the aorta was detected by 4 hours after injury and was most marked over the first 24 hours, as estimated by increases in concentration of fibrinopeptide A during incubation of segments with recalcified barium-adsorbed plasma or activity against the thrombin-synthetic substrate S-2238. Based on comparison with purified human thrombin incubated under the same conditions, a maximum of 0.04 to 0.1 nmol/L per square centimeter of thrombin activity was associated with the vascular wall during the first 24 hours and remained detectable for 72 hours. In contrast, bound Xa/Va complex activity to injured segments was detected within 15 minutes and induced activation of **prothrombin** added to recalcified barium-adsorbed plasma incubated with injured segments for 96 hours. Aspirin (15 mg/kg) administered 30 minutes before injury attenuated 111In-**platelet** deposition at 4 hours by 67%, with an associated decrease in bound Xa/Va and thrombin activity at 15 minutes and 4 hours. However, intravenous heparin did not attenuate bound Xa/Va activity at 15 minutes or thrombin activity at 15 minutes and 4 hours. **Platelet**-dependent bound Xa/Va activity occurs rapidly after arterial injury and may promote thrombin elaboration for up to 96 hours. Bound thrombin activity and de novo thrombin elaboration on the vascular wall may play an important role in the progression of thrombosis and vascular wall remodeling.

L12 ANSWER 12 OF 19 EMBASE on STN
ACCESSION NUMBER: 1998358055 EMBASE
TITLE: The use of low-molecular-weight heparins in cardiovascular disease.
AUTHOR: Verhaeghe R.
CORPORATE SOURCE: R. Verhaeghe, U.Z. Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium
SOURCE: Acta Cardiologica, (1998) 53/1 (15-21).
Refs: 39
ISSN: 0001-5385 CODEN: ACCAAQ
COUNTRY: Belgium
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index

Searcher : Shears 571-272-2528

039 Pharmacy
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Unfractionated heparin (UFH) has been used for decades as an effective and relatively inexpensive agent in the prevention of venous and arterial thromboembolic events. Low-molecular-weight heparin (LMWH) preparations are obtained by chemical or enzymatic depolymerization of unfractionated commercial grade heparin; their mean molecular weights range from below 4000 to about 6500 D (Table 1). Their mechanism of antithrombotic action is basically similar to that of UFH - binding to antithrombin to inhibit activated coagulation factors - but they have a different relative potency (to some extent also inter-individually) of anti-Xa versus anti-IIa activity. Shorter fragments which contain the essential pentasaccharide to bind to antithrombin but lack the required chain length to bind at the same time to thrombin, only inhibit activated Factor X. Fragments above 5000 D which contain the pentasaccharide maintain their property to inhibit Factor Xa but with increasing chain length, they become stronger inhibitors of thrombin. LMWHs have little or no effect on global tests of blood coagulation such as the activated partial thromboplastin time when used in prophylactic or therapeutic dosages. A specific assay of anti-Xa activity is required to monitor biological activity but this is rarely needed. The main advantage of LMWHs for clinical practice derive from their pharmacokinetic properties. UFH binds to plasma proteins, endothelial cells and **platelets**. This saturable mechanism clears heparin rapidly from the circulation (the plasma half-life is non-linearly dose-related) and is held responsible for the large variation from person to person and from moment to moment in biological and clinical response. LMWHs bind far less to these elements and therefore have a 2 to 4-times longer plasma half-life, a markedly better bioavailability when injected subcutaneously and a more stable dose response. They also have a lower toxic effect in terms of heparin-induced thrombocytopenia which may be related to their lesser interaction with **platelets**.

L12 ANSWER 13 OF 19 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:64035 SCISEARCH
THE GENUINE ARTICLE: YQ442
TITLE: New insights into the regulation of the blood clotting cascade derived from the X-ray crystal structure of bovine meizothrombin des F1 in complex with PPACK
AUTHOR: Martin P D (Reprint); Malkowski M G; Box J; Esmon C T; Edwards B F P
CORPORATE SOURCE: WAYNE STATE UNIV, DEPT BIOCHEM & MOL BIOL, DETROIT, MI 48201 (Reprint); OKLAHOMA MED RES FDN, HOWARD HUGHES MED INST LABS, OKLAHOMA CITY, OK 73104
COUNTRY OF AUTHOR: USA
SOURCE: STRUCTURE, (15 DEC 1997) Vol. 5, No. 12, pp. 1681-1693.
Publisher: CURRENT BIOLOGY LTD, 34-42 CLEVELAND STREET, LONDON, ENGLAND W1P 6LB.
ISSN: 0969-2126.
DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 70
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The conversion of **prothrombin** to thrombin by factor Xa is the penultimate step in the blood clotting cascade. In vivo, where the conversion occurs primarily on activated **platelets** in association with factor Va and Ca2+ ions, meizothrombin is the major intermediate of the two step reaction, Meizothrombin rapidly loses the fragment 1 domain (F1) by autolysis to become meizothrombin des F1 (mzTBN-F1). The physiological properties of mzTBN-F1 differ dramatically from those of thrombin due to the presence of **prothrombin** fragment 2 (F2), which remains covalently attached to the activated thrombin domain in mzTBN-F1.

Results: The crystal structure of mzTBN-F1 has been determined al 3.1 Angstrom resolution by molecular replacement, using only the thrombin domain, and refined to R and R-free values of 0.205 and 0.242, respectively. The protease active site was inhibited with o-Phe-Pro-Arg-chloromethylketone (PPACK) to reduce autolysis. The mobile linker chain connecting the so-called kringle and thrombin domains and the first two N-**acetylglucosamine** residues attached to the latter were seen in electron-density maps improved with the program SQUASH. Previously these regions had only been modeled.

Conclusions: The F2 kringle domain in mzTBN-F1 is bound to the electropositive heparin-binding site on thrombin in an orientation that is systematically shifted and has significantly more interdomain contacts compared to a noncovalent complex of free F2 and free thrombin. F2 in mzTBN-F1 forms novel hydrogen bonds to the carbohydrate chain of thrombin and perhaps stabilizes a unique, rigid conformation of the gamma-autolysis loop through non-local effects. The F2 linker chain, which does not interfere with the active site or fibrinogen-recognition site, is arranged so that the two sites cleaved by factor Xa are separated by 36 Angstrom. The two mzTBN-F1 molecules in the asymmetric unit share a tight 'dimer' contact in which the active site of one molecule is partially blocked by the F2 kringle domain of its partner. This interaction suggests a new model for **prothrombin** organization.

L12 ANSWER 14 OF 19 EMBASE on STN

ACCESSION NUMBER: 97087490 EMBASE
DOCUMENT NUMBER: 1997087490
TITLE: Pharmacodynamic models to evaluate antithrombotics in clinical pharmacology.
AUTHOR: Muller T.H.
CORPORATE SOURCE: Dr. T.H. Muller, Institute Oldenburg, GRCBTS, Brandenburger Str. 21, D-28133 Oldenburg, Germany
SOURCE: Journal of Clinical Pharmacology, (1997) 37/1 SUPPL. (49S-58S).
Refs: 77
ISSN: 0091-2700 CODEN: JCPCBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular

Surgery
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The need to prevent thromboembolic events effectively and safely has stimulated an intense search for novel antithrombotics. Parameters derived from in vitro tests with patients' blood are essential for therapeutic monitoring of anticoagulants. Clinical pharmacologic evaluation of novel antithrombotic therapies based on such parameters can easily fail, however, by neglecting pivotal pathophysiologic determinants of thrombus formation. When vascular injury occurs, blood cells, plasma proteins, and the vessel wall intimately cooperate for an adequate local repair. Much remains to be learned about the local and transient interaction of these components. In most tests of **platelet** function and coagulation proteins, blood samples from treated individuals are stimulated in vitro to assess inhibitory effects. Limitations of such a test strategy for dosefinding studies with antithrombotics may be overcome by measuring activation markers specifically generated on the surface of blood cells or in plasma at the site of thrombosis in patients.

L12 ANSWER 15 OF 19 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 93004763 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1391958
TITLE: Antiplatelet drugs and generation of thrombin in clotting blood.
AUTHOR: Szczeklik A; Krzanowski M; Gora P; Radwan J
CORPORATE SOURCE: Department of Medicine, Copernicus Academy of Medicine, Cracow, Poland.
SOURCE: Blood, (1992 Oct 15) 80 (8) 2006-11.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19980206
Entered Medline: 19921118

AB **Platelets** participate in formation of thrombin through secretion of coagulation factors and by providing a catalytic surface on which **prothrombinase** complex is assembled. We studied the effects of four antiplatelet drugs on thrombin formation in healthy volunteers. Thrombin generation was monitored both in vitro--in recalcified plasma--and ex vivo--in blood emerging from a standardized skin microvasculature injury, which also served to determine bleeding time. A mathematical model has been developed to describe the latter reaction. It is based on estimation of the rate of increase in fibrinopeptide A (FPA), a specific marker of thrombin activity, in blood emerging from skin incisions. Two hours after

the ingestion of 500 mg of aspirin, thrombin formation became significantly impaired both in vitro and ex vivo. In contrast, 2 hours after the oral administration of placebo, indomethacin 50 mg, or OKY-046 (a thromboxane synthase inhibitor) 400 mg, thrombinogenesis remained unaltered. Ticlopidine, studied either 3 hours after 500 mg oral administration, or after 5 days of intake at a daily dose of 500 mg, had no effect on thrombin generation. Thus, aspirin, contrary to other antiplatelet drugs, depresses thrombin formation in clotting blood, a phenomenon that might be of clinical relevance. It is suggested that aspirin exerts this effect by **acetylating prothrombin** and/or macromolecules of **platelet** membrane.

L12 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1992:458202 BIOSIS
DOCUMENT NUMBER: PREV199294099602; BA94:99602
TITLE: THE IN-VIVO EFFECT IN HUMANS OF **PYRIDOXAL** -5'-**PHOSPHATE** ON **PLATELET** FUNCTION AND BLOOD COAGULATION.
AUTHOR(S): VAN WYK V [Reprint author]; LUUS H G; HEYNS A D P
CORPORATE SOURCE: DEP HAEMATOL, UNIV ORANGE FREE STATE, PO BOX 339, BLOEMFONTEIN 9300, SOUTH AFRICA
SOURCE: Thrombosis Research, (1992) Vol. 66, No. 6, pp. 657-668.
CODEN: THBRAA. ISSN: 0049-3848.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Oct 1992
Last Updated on STN: 8 Oct 1992

AB Vitamin B6 has an antithrombotic effect. This, based on the results of in vitro studies, has been attributed to an antiplatelet effect. We assessed the in vivo effect of vitamin B6 by measuring the effect of long-term administration of vitamin B6 on **platelet** function and blood coagulation. Vitamin B6 (pyridoxine hydrochloride), 100mg twice daily p.o. for fifteen days, was administered to 10 healthy volunteers. The bleeding time was measured before the first dose and 15 days after. A baseline value, the acute effect, chronic effect, and the acute-on-chronic effect of vitamin B6 was estimated by measuring **platelet** function. The following tests were performed: **platelet** aggregation induced by collagen, ADP and epinephrine; thromboxane A2 (TXA2)-production and prostacyclin inhibition of ADP-induced aggregation. The effects on the coagulation system were monitored by measuring: the **prothrombin** time, activated partial thromboplastin time and levels of coagulation factor. Vitamin B6 significantly prolonged the bleeding time from 4.1 ± 1.1 minutes to 6.8 ± 1.0 minutes ($p = 0.0063$). Aggregation of **platelets** with collagen was slightly but not significantly inhibited. **Platelet** aggregation induced with the agonists ADP or epinephrine was significantly inhibited by vitamin B6, and the **platelets** tended to aggregate at a slighty decreased rate. The mean TxA2-production was slightly, but not significantly, decreased. Vitamin B6 had no effect on the sensitivity of **platelets** to prostacyclin, or on the coagulation system.

Our results indicate that the antithrombotic effects of vitamin B6 is limited to inhibition of **platelet** function; there was no measurable influence on coagulation. The results of this in vivo study are however such that clinical trials are warranted to further assess the efficacy of vitamin B6 as an antiplatelet drug.

L12 ANSWER 17 OF 19 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 86097695 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4082107
TITLE: Comparison of the abilities of synthetic and **platelet**-derived membranes to enhance thrombin formation.
AUTHOR: Jones M E; Lentz B R; Dombrose F A; Sandberg H
CONTRACT NUMBER: HL22771 (NHLBI)
SOURCE: Thrombosis research, (1985 Sep 15) 39 (6) 711-24. Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860129

AB The relative abilities of **platelet**-derived membranes and synthetic phospholipid vesicles to enhance the **prothrombinase**-catalyzed conversion of **prothrombin** to thrombin have been determined. For each type of membrane, the maximum amount of thrombin formed as a function of amount of available lipid was measured using a chromogenic substrate assay. The lipid concentration at which the amount of thrombin formed began to exceed that formed in the absence of lipid (critical phospholipid concentration) was used to compare the surfaces' abilities to support thrombin formation. For **platelet**-derived membranes and for equimolar, charged-lipid/phosphatidylcholine (PC) vesicles, the critical concentrations increased in the following order: **platelet**-derived membranes approximately equal to phosphatidylserine (PS) approximately equal to phosphatidic acid (PA) less than monomethyl PA and monoethyl PA much less than phosphatidylinositol and phosphatidylglycerol. For mixed anionic/neutral lipid vesicles above their phase transitions, measured critical concentrations were relatively insensitive to changes in lipid **acyl** chains, the neutral lipid component, and membrane curvature but were sensitive to changes in the anionic lipid content of the mixtures. Comparison of these data suggested that equimolar PS/PC and PA/PC vesicles can emulate reasonably well the thrombin-generating ability of **platelet**-derived membranes.

L12 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1982:152260 BIOSIS
DOCUMENT NUMBER: PREV198273012244; BA73:12244
TITLE: **ACETYL** SALICYLIC-ACID AS AN ANTI THROMBO EMBOLIC AGENT.
AUTHOR(S): KETSA-ARD K [Reprint author]; NA AYDHYA Q D

CORPORATE SOURCE: DEP OF PHARMACOLOGY, SIRIRAJ HOSPITAL, MAHIDOL UNIV, BANGKOK, THAILAND
SOURCE: Siriraj Hospital Gazette, (1980) Vol. 32, No. 11, pp. 667-674.
CODEN: SHGAB8. ISSN: 0125-152X.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: THAI

AB **Acetylsalicylic** acid (aspirin) impaired **platelet** function in vitro and in vivo. The observations were made in humans after different administration of aspirin. A single dose of 600 mg aspirin was given once a week for 6 wk in 16 normal subjects and 4 patients of thromboembolism. Another 15 normal subjects took 300 mg aspirin after meals 3 times a day. Measurement of **platelet** aggregation by ADP and by adrenaline [epinephrine] was done in all subjects after the last dose of aspirin. Inhibition of **platelet** aggregation was achieved, degree and duration of inhibition was in the same range after weekly or daily doses of aspirin. The effect of aspirin on **platelet** aggregation after the last dose could be maintained longer than 1 wk in 31 of 35 subjects. The 600 mg aspirin per wk did not significantly change the **prothrombin** time and partial thromboplastin time. In human subjects, 600 mg aspirin per wk was effective in impairing **platelet** aggregation and was considered to be safe.

L12 ANSWER 19 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1977:187927 BIOSIS
DOCUMENT NUMBER: PREV197764010291; BA64:10291
TITLE: THE EFFECT OF A NEW NONSTEROIDAL ANTI INFLAMMATORY AGENT SULINDAC ON **PLATELET** FUNCTION.
AUTHOR(S): GREEN D; GIVEN K M; TS'AO C-H; WHIPPLE J P; ROSSI E C
SOURCE: Thrombosis Research, (1977) Vol. 10, No. 2, pp. 283-289.
CODEN: THBRAA. ISSN: 0049-3848.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: Unavailable

AB Sulindac, a new non-steroidal anti-inflammatory agent, was investigated in parallel with ASA [**acetylsalicylic** acid] and indomethacin for its effects on **platelet** function. In vitro, in concentrations of 0.28 mM, the drug inhibited collagen-induced **platelet** aggregation without significantly affecting epinephrine-induced aggregation. ASA, indomethacin and the sulfide metabolite of sulindac inhibited both collagen and epinephrine-induced aggregation. When all compounds were tested at a concentration of 0.14 mM, only sulindac did not inhibit collagen-induced release of 14C-serotonin. A randomized, double-blind trial of sulindac, ASA and placebo demonstrated that inhibition of collagen-induced **platelet** aggregation by sulindac was transient, disappearing 24 h after administration of the last dose of the drug. Inhibition by ASA persisted for > 24 h. Similar findings were noted in studies of **platelet** release of 14C-serotonin. As compared with the placebo group, the bleeding time was significantly prolonged 6 h after ingestion of ASA but not after sulindac. Sulindac was clinically well-tolerated, while

gastrointestinal complaints were common in subjects taking aspirin. Like ASA, sulindac administration caused no important changes in the clotting time, clot retraction, **prothrombin** time, partial thromboplastin time or fibrinogen levels. Thus, in comparison with common anti-inflammatory drugs, sulindac is shown to be a moderate to weak inhibitor of **platelet** function.

(FILE 'REGISTRY' ENTERED AT 12:04:03 ON 26 MAY 2004)
E FACTOR XA/CN 5
L15 1 S E3
E FACTOR VA/CN 5
L16 2 S E3
L17 3 S L15 OR L16

FILE 'HCAPLUS' ENTERED AT 12:04:29 ON 26 MAY 2004
L1 6 SEA FILE=REGISTRY ABB=ON PLU=ON (PROTHROMBIN/CN OR "PROTHROMBIN (CHICKEN CLONE PCII 203)"/CN OR "PROTHROMBIN (HUMAN CLONE L(14,25,33,36,81) GENE F2)"/CN OR "PROTHROMBIN (OSTRICH)"/CN OR "PROTHROMBIN (RABBIT)"/CN OR "PROTHROMBIN (ZEBRAFISH)"/CN)
L2 7 SEA FILE=REGISTRY ABB=ON PLU=ON (PROTHROMBINASE/CN OR "PROTHROMBINASE (HUMAN CLONE HFGL2 GENE FGL2)"/CN OR "PROTHROMBINASE (HUMAN GENE FGL-2)"/CN OR "PROTHROMBINASE (HUMAN GENE FGL2)"/CN OR "PROTHROMBINASE (MOUSE GENE FGL-2)"/CN OR "PROTHROMBINASE (MOUSE MACROPHAGE CLONE 11-3-1 GENE MUSFIBLP)"/CN OR "PROTHROMBINASE (RATTUS NORVEGICUS STRAIN SPRAGUE-DAWLEY GENE FGL-2 SEQUENCE HOMOLOG)"/CN OR "PROTHROMBINASE (SWINE GENE FG12)"/CN)
L3 32 SEA FILE=REGISTRY ABB=ON PLU=ON (THROMBIN/CN OR "THROMBIN (ACIPENSER TRANSMONTANUS B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (AGKISTRODON HALYS USSURIENSIS VENOM GLAND)"/CN OR "THROMBIN (AGKISTRODON RHODOSTOMA VENOM CLONE PCL28BPV-FIBROGENASEI PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (AGKISTRODON RHODOSTOMA VENOM CLONE PCL28BPV-FIBROGENASEII FRAGMENT REDUCED)"/CN OR "THROMBIN (AGKISTRODON RHODOSTOMA VENOM CLONE PCL28BPV-FIBROGENASEIII FRAGMENT REDUCED)"/CN OR "THROMBIN (AGKISTRODON RHODOSTOMA VENOM CLONE PCL28BPV-FIBROGENASEIV FRAGMENT REDUCED)"/CN OR "THROMBIN (CATTLE SUBUNIT A)"/CN OR "THROMBIN (CATTLE SUBUNIT B PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (CHICKEN B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (CYNOPS PYRRHOGASTER B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (EPTATRETUS STOUTI B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (GEKKO GEKKO B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (HUMAN CLONE L25/L36 A-SUBUNIT)"/CN OR "THROMBIN (HUMAN CLONE L25/L36 B-SUBUNIT PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (HUMAN CLONE L25/L36 PROTEIN MOIETY)"/CN OR "THROMBIN (HUMAN LIVER)"/CN OR "THROMBIN (HUMAN-A)"/CN OR "THROMBIN (HUMAN-B REDUCED)"/CN OR "THROMBIN (LACHESIS STENOPHRYS VENOM FRAGMENT)"/CN OR "THROMBIN (MOUSE B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (MOUSE CLONE MII17B/MC3 A-SUBUNIT)"/CN OR "THROMBIN (MOUSE CLONE MII17B/MC3 B-SUBUNIT PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (MOUSE CLONE MII17B/MC3

PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (ONCORHYNCHUS MYKISS B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (ONCORHYNCHUS MYKISS LIVER C-TERMINAL FRAGMENT) "/CN OR "THROMBIN (OX SUBUNIT A)"/CN OR "THROMBIN (OX SUBUNIT B PROTEIN MOIETY REDUCED)"/CN OR "THROMBIN (RABBIT B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (RAT B-SUBUNIT C-TERMINAL FRAGMENT REDUCED)"/CN OR "THROMBIN (SYNTHETIC HUMAN CLONE WO-02/100337A2-SEQID 1)"/CN OR "THROMBIN (SYNTHETIC HUMAN CLONE WO-02/100337A2 -SEQID2)"/CN OR "

L4	31184	SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR PROTHROMBIN OR FACTOR(W)(2 OR II)
L5	1481	SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (L2 OR PROTHROMBINASE)
L13	160	SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (ACTIVAT?(S)PLATELET OR PAS(S)PLATELET)
L14	125	SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND (L3 OR THROMBIN OR THROMBASE)
L15	1	SEA FILE=REGISTRY ABB=ON PLU=ON "FACTOR XA"/CN
L16	2	SEA FILE=REGISTRY ABB=ON PLU=ON "FACTOR VA"/CN
L17	3	SEA FILE=REGISTRY ABB=ON PLU=ON L15 OR L16
L18	106	SEA FILE=HCAPLUS ABB=ON PLU=ON L14 AND (L17 OR FACTOR(W)(XA OR VA))
L19	22	SEA FILE=HCAPLUS ABB=ON PLU=ON L18 AND ASSAY?
L20	18	SEA FILE=HCAPLUS ABB=ON PLU=ON L19 AND (MEAS? OR QUANT? OR DETERM? OR DETECT? OR DET##)

L21 15 L20 NOT L10

L21 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 Mar 2004
ACCESSION NUMBER: 2004:209506 HCAPLUS
DOCUMENT NUMBER: 140:314782
TITLE: Recombinant factor VIIa partially reverses the inhibitory effect of fondaparinux on **thrombin** generation after tissue factor **activation** in **platelet** rich plasma and whole blood
AUTHOR(S): Gerotziafas, Grigoris T.; Depasse, Francois; Chakroun, Tahar; Samama, Meyer M.; Elalamy, Ismail
CORPORATE SOURCE: Service d'Hematologie Biologique, Hopital Hotel-Dieu de Paris, Paris, 75181, Fr.
SOURCE: Thrombosis and Haemostasis (2004), 91(3), 531-537
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fondaparinux (Arixtra), a specific AT-dependent FXa inhibitor, is effective and safe in the prevention and treatment of venous thromboembolism, but some major hemorrhagic events may occur. No specific antidote to fondaparinux has been proposed. Recombinant FVIIa (Novoseven) could be used as an hemostatic treatment, but this option has not been well documented. We studied the effect of rFVIIa (1 μg/mL) on the inhibition of **thrombin**

generation induced by fondaparinux (0.1 μg/mL to 1 μg/mL). Coagulation was triggered in platelet rich plasma (PRP) or in whole blood by recalcification in the presence of diluted thromboplastin. In PRP **thrombin** generation was assessed using the thrombinoscope **assay**. In whole blood, **prothrombin** activation was assessed by **measuring** the kinetics of F1+2 formation using an ELISA **assay**. Fondaparinux at concns. equal or greater than 0.5 μg/mL prolonged the initiation phase of **thrombin** generation, and reduced the velocity of **prothrombin** activation. It also decreased by 60% the endogenous **thrombin** potential. In the presence of fondaparinux (0.5 μg/mL to 1 μg/mL) rFVIIa accelerated the initiation phase of **thrombin** generation, but it did not significantly increase the endogenous **thrombin** potential. However, rFVIIa did not completely reverse the inhibitory effect of fondaparinux on the parameters of **thrombin** generation and **prothrombin** activation. This study shows that rFVIIa accelerates **thrombin** generation, but does not completely reverse the inhibitory effect of fondaparinux on **thrombin** generation. The potential clin. use of rFVIIa as hemostatic treatment of major bleedings related to fondaparinux has to be evaluated.

IT **9002-04-4, Thrombin 9002-05-5, Factor Xa**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (recombinant factor VIIa partially reverses fondaparinux-induced inhibition of **thrombin** generation after tissue factor activation)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Jul 2003
ACCESSION NUMBER: 2003:522128 HCAPLUS
DOCUMENT NUMBER: 139:211400
TITLE: **Platelet activation** in a circulating flow loop: Combined effects of shear stress and exposure time
AUTHOR(S): Jesty, Jolyon; Yin, Wei; Perrotta, Peter; Bluestein, Danny
CORPORATE SOURCE: Division of Hematology, School of Medicine, Stony Brook University, Stony Brook, NY, USA
SOURCE: Platelets (2003), 14(3), 143-149
CODEN: PLTEEF; ISSN: 0953-7104
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Measurement** of small changes in **platelet activation** state (**PAS**) in circulating stenotic systems in vitro has been problematic because of a paucity of real-time **assay** methods and circulation systems of low **platelet-activating** potential. **PAS** was **measured** by a modified **prothrombinase assay** in which **activated platelets** provide the essential cofactors in the **activation** of

prothrombin by **factor Xa**. Chemical modification of the **prothrombin** ensures that the **thrombin** produced, while **assayable**, does not **activate platelets**. Human platelets were circulated in loops in which exposure to shear stress was adjusted by independently varying flow rate, viscosity, and the time of exposure to shear. Although with some differences in **platelet** response to different conditions of stress, the **PAS** directly increased with time of circulation, shear stress, and time of exposure to shear. The results show that low-level **platelet activation** caused by shear stress in a circulation loop can be **quant.** assessed in near-real time in a system of tube geometry. They confirm previous results obtained in non-circulating systems that exposure of **platelets** to shear conditions on the same order as found in the vasculature causes significant **platelet activation**, and that this **activation** is dependent on both shear stress and time of exposure.

IT **9001-26-7, Prothrombin 9002-04-4, Thrombin 9002-05-5, Factor Xa 72162-96-0, Prothrombinase**
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(use in **measuring platelet activation** state; method for **measuring** human **platelet activation** in circulating flow loop and combined effects of shear stress and exposure time on **platelet activation**)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Feb 2000
ACCESSION NUMBER: 2000:84984 HCAPLUS
DOCUMENT NUMBER: 133:29106
TITLE: Course of molecular hemostatic markers during and after different surgical procedures
AUTHOR(S): Siemens, H.-J. G.; Brueckner, S.; Hagelberg, S.; Wagner, T.; Schmucker, P.
CORPORATE SOURCE: Department of Anesthesiology, Subdivision of Hematology, 1st and 2nd Department of Internal Medicine, Medical University of Lubeck, Lubeck, Germany
SOURCE: Journal of Clinical Anesthesia (1999), 11(8), 622-629
CODEN: JCLBE7; ISSN: 0952-8180
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The most vulnerable time of thrombi formation was studied with regard to the plasmatic (noncellular) part of the coagulatory and fibrinolytic systems by a nonrandomized observational study. There were studied 61 consenting ASA phys. status I and II inpatients undergoing 4 different types of surgery: total hip replacement

(THR): 16 patients; hemicolectomy: 15 patients; endoscopic cholecystectomy: 15 patients; subtotal thyroid resection: 15 patients. The time course of 11 procoagulatory and fibrinolytic parameters was examined during the different types of surgery. Blood samples were drawn on the day before surgery, directly before the induction of general anesthesia, 1-2 h postoperatively, and on the mornings of postoperative days 1, 2, 3, 4, and 5. The coagulation samples were centrifuged within 1 h of collection at 2,300 g for 15 min at 4°. Hb, hematocrit, **platelets**, fibrinogen, **prothrombin** time, **activated** partial thromboplastin time, **thrombin** time, antithrombin III, and protein C were **determined** immediately on laboratory arrival of the samples. The samples were aliquoted at -70°. They were thawed within 2 wk and prepared for the following **assays: thrombin** -antithrombin III complexes (TAT-complexes), D-dimers, and plasminogen activator inhibitor type 1. Maximum activation of coagulation is not reached until 2 h postoperatively and slowly decreases until normal values are reached around the 5th postoperative day. Parameters displaying the greatest changes are TAT-complexes and D-dimers. The type of surgery with the most pronounced changes was total hip replacement, followed by hemicolectomy, cholecystectomy, and subtotal thyroid resection. The total hip replacement and hemicolectomy groups show similar and strong activation of the procoagulatory and fibrinolytic systems. Much less pronounced are the changes during endoscopic cholecystectomy and subtotal thyroid resection. Maximum activation occurs 1-2 h postoperatively.

IT **9002-04-4, Thrombin**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(complex with antithrombin III; mol. hemostatic markers during and after different surgical procedures)

IT **9001-26-7, Prothrombin 9002-05-5,** Thromboplastin
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(mol. hemostatic markers during and after different surgical procedures)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 23 Jan 2000
ACCESSION NUMBER: 2000:52857 HCAPLUS
DOCUMENT NUMBER: 132:329669
TITLE: Inactivation of **factor Xa** by the synthetic inhibitor DX-9065a causes strong anticoagulant and antiplatelet actions in human blood
AUTHOR(S): Kaiser, B.; Jeske, W.; Walenga, J. M.; Fareed, J.
CORPORATE SOURCE: Center for Vascular Biology and Medicine Erfurt, Friedrich Schiller University Jena, Erfurt, D-99089, Germany
SOURCE: Blood Coagulation & Fibrinolysis (1999), 10(8),

495-501
CODEN: BLFIE7; ISSN: 0957-5235
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an in vitro study, anticoagulant and antiplatelet effects of the synthetic, direct **factor Xa** inhibitor DX-9065a, (+)-2S-2-[4-[[(3S)-1 acetimidoyl-3-pyrrolidinyl]oxy]phenyl]-3-[7-amidino-2-naphthyl]propanoic acid hydrochloride pentahydrate, which shows a high affinity and selectivity towards the enzyme, were investigated. Anticoagulant actions of DX-9065a were studied in human plasma using global clotting **assays** [**prothrombin** time (PT), activated partial thromboplastin time (APTT), **thrombin** time (TT) and Heptest]. The effect on **thrombin** generation was **measured** in whole blood by **determining** the plasma concentration of **prothrombin** fragment F1.2. The influence on agonist-induced **platelet activation** in whole blood was studied using flow cytometric anal. DX-9065a caused a concentration-dependent prolongation of clotting times in the PT and APTT **assay**, whereas Heptest was less affected and TT was not influenced. Furthermore, DX-9065a strongly inhibited the generation of **thrombin** without and after coagulation activation. The **factor Xa** inhibitor did not affect **platelet activation** mediated by either **thrombin** receptor **activating** peptide, arachidonic acid or γ- **thrombin**, but prevented tissue factor- and **factor Xa**-induced **activation** of **platelets** in a concentration-dependent manner. Inactivation of **factor Xa** by a highly effective and selective inhibitor, and the resulting inhibition of **thrombin** generation leads to strong anticoagulant and antiplatelet actions. The interference with the coagulation system at the early level of **factor Xa** is expected to be an effective approach for a successful anticoagulant/antithrombotic therapy.

IT **9002-05-5, Factor Xa**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inactivation of **factor Xa** by the synthetic inhibitor DX-9065a causes strong anticoagulant and antiplatelet actions in human blood)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 22 Nov 1999
ACCESSION NUMBER: 1999:741547 HCAPLUS
DOCUMENT NUMBER: 131:349836
TITLE: APTT revisited. **Detecting** dysfunction in the hemostatic system through waveform analysis
AUTHOR(S): Toh, Cheng Hock
CORPORATE SOURCE: Dep. Hematology, Royal Hospital, Liverpool Univ., Liverpool, L7 8XP, UK
SOURCE: Thrombosis and Haemostasis (1999), 82(2), 684-687

CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The transmittance waveform (TW) patterns of the activated partial thromboplastin time (ATTP) **assay** were investigated to identify disseminated intravascular coagulation (DIC) at an early stage. ATTP TW investigations were performed on the multi channel discrete analyzer (MDA) 180 with the optics set at 580 nm. All patients who had DIC showed a characteristic biphasic APTT TW profile. When the APTT TW was examined in all consecutively received samples through the routine hospital coagulation laboratory, 54 patients were found with biphasic APTT TWs. 40 Of these had DIC, and the remaining 14 patients with biphasic APTT TW showed some evidence of coagulation activation with abnormalities. Overall, the sensitivity and specificity of the biphasic waveform for DIC was 97.6% and 98%, resp. The pos. predictive value of the test was 74%, which increased with increasing steepness of the biphasic slope. It is concluded that the APTT TW fulfills the requirements for a simple, rapid, and robust **assay** in DIC.

IT **9001-26-7, Prothrombin 9002-04-4, Thrombin 9002-05-5,** Thromboplastin
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(disseminated intravascular coagulation early stage diagnosed by transmittance waveform of activated partial thromboplastin time)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 22 Jun 1998
ACCESSION NUMBER: 1998:381603 HCAPLUS
DOCUMENT NUMBER: 129:23201
TITLE: Inhibition of **thrombin**-catalyzed factor V activation by bothrojaracin
AUTHOR(S): Arocas, Veronique; Lemaire, Charlotte; Bouton, Marie-Christine; Bezeaud, Annie; Bon, Cassian; Guillin, Marie-Claude; Jandrot-Perrus, Martine
CORPORATE SOURCE: Lab. Recherche Hemostase Thrombose, Fac. Med. Xavier Bichat, Univ. Paris, Paris, F-75870, Fr.
SOURCE: Thrombosis and Haemostasis (1998), 79(6), 1157-1161
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **thrombin** inhibitor bothrojaracin from Bothrops jararaca interacts with the 2 pos. charged recognition sites of **thrombin** referred to as exosite 1 and exosite 2, whereas it does not interact with the **thrombin** active site. Bothrojaracin inhibits **thrombin**-induced fibrinogen to fibrin conversion and **platelet activation,** without inhibition of **thrombin**-catalyzed cleavage of small synthetic substrates. Bothrojaracin exerts an anticoagulant effect